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14. ABSTRACT People differ in their susceptibility to abuse alcohol and drugs, and the conditions that lead to abuse and dependence are not the same in everyone. Some people are susceptible because they experience particularly positive effects from alcohol and drugs; often, the same people have problems controlling their behavior. They are impulsive; they seek out novel and exciting experiences; and they may be influenced by other rewards, such as those associated with gambling or risky sexual behavior, even if the long-term consequences of those behaviors are harmful. This study will evaluate the relationship between the response to a stimulant drug and behavioral control. First, we will administer 10 mg *d*-amphetamine and select two groups of individuals: a group that reports strong stimulant effects (*Responders*) and a group that reports no stimulant effects (*Nonresponders*). Next we will record event-related brain potentials (ERPs) while participants perform tasks that tap aspects of behavioral control: response inhibition, novelty detection, and reward processing. To evaluate the neural mechanisms involved in these processes, we will record ERPs after placebo, and in a separate session, after 10 mg *d*-amphetamine. This research will identify aspects of control that differentiate these groups and elucidate the neural systems that mediate these differences. As such, the findings of this research may lead to better treatments for alcohol and drug abuse, particularly for people who abuse these drugs because of their stimulating effects.

15. SUBJECT TERMS
event-related brain potentials (ERPs), stop P3, error-related negativities, P300, P3a, reorienting negativity (RON), response inhibition, reward processing, novelty detection, error-processing, vulnerability marker, cognitive control, amphetamine

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PR065029 Cooperative Agreement

Amphetamine Challenge:
A Marker of Brain Function that Mediates Risk for Drug and Alcohol Abuse

Principal Investigator: Frances H. Gabbay, Ph.D.
Co-Investigator: Connie C. Duncan, Ph.D.

Annual Report (No. 2)

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Introduction

People differ widely in their susceptibility to abuse alcohol and other drugs, and the conditions that lead to abuse and dependence may not be the same in all people. Some people are susceptible because they experience particularly positive effects from alcohol and drugs—the drugs make them feel good. Often, the same people who experience these very positive effects also have problems controlling their behavior. They are impulsive—it may be difficult for them to stop a behavior, even if they realize it could lead to a bad outcome. They seek out novel and exciting experiences, often without considering the consequences, and are often influenced by other rewards. They do things that may lead to short-term rewards, such as gambling or risky sexual behavior, even if the long-term consequences may be harmful. When these characteristics occur together, individuals are more likely to try alcohol or drugs at a young age, to use these substances more heavily, to continue their use, and to develop problems related to their use. We do not know why some people experience more positive—or stimulating—effects of alcohol and drugs, or why this characteristic is sometimes associated with poor control. Using cognitive tasks that invoke specific aspects of behavioral control, it is possible to assess in the laboratory aspects of behavioral control related to risk for alcohol and drug abuse. Event-related brain potentials (ERPs) recorded during performance of these tasks permit evaluation of concomitant neural processing. Thus, in the first phase of this study, we administer to young men and women 10 mg *d*-amphetamine, a drug with stimulant effects that are similar to those of alcohol and other drugs. We record the effects of the drug on their mood, and select a group of people who experience strong, positive feelings from the drug (*Responders*) and a group of people who do not (*Nonresponders*). Then, in two separate sessions, we record ERPs while individuals in these two groups perform tasks designed to tap aspects of behavioral control: response inhibition, novelty detection, and reward sensitivity. In one of the two sessions, we administer a placebo; in a separate session, we administer 10 mg *d*-amphetamine. The research will identify aspects of behavioral control that differentiate *Responders* and *Nonresponders*, and elucidate the cognitive and neural bases of these differences. The results of this study will help us to understand the association between stimulant drug response and behavioral control (i.e., why they occur together in people and how they lead to poor decisions about alcohol and drug use). Thus, the findings of this research may lead to better treatments for alcohol and drug abuse, particularly for people who abuse these drugs because of their stimulating effects, and who make impulsive decisions about using these substances.

Body: Progress and Problems

Progress. In this section, we state progress made on each of the tasks listed in our *Statement of Work*. To summarize, we obtained HSRRB approval on 7/03/08, for the protocol as well as for amendments that reflect improvements to the original protocol. The latter were detailed in our first annual report. In the time since obtaining approval, we have focused on recruiting, screening, and testing participants, and on processing data collected during the testing.

Task 1: Submit protocol to local (USU) Institutional Review Board (IRB). **DONE**

a. Develop and submit protocol, informed consent documents, and other supporting materials, including questionnaires and other study forms, to IRB. **DONE**
b. Provide IRB approval letter to USAMRAA. **DONE**

Task 2: Submit protocol and supporting materials to USAMRMC Human Subjects Research Review Board (HSRRB) and obtain HSRRB approval. **DONE**.

Task 3: Engineer modifies software used to run the cognitive tasks to meet study specifications (Months 1–3). **DONE**

Task 4: Preparations for testing. **DONE**

a. Recruit research assistants. **DONE**
b. Recruit nurse practitioner. **DONE**
c. Train research assistants in all procedures for the study. **DONE**
d. Order laboratory supplies and set up laboratory. **DONE.**

Task 5: Recruitment and screening. **IN PROGRESS**

a. Place advertisements **CONTINUOUS**
b. Field responses to advertisements **CONTINUOUS**

Task 6: Conduct web-screening of 2,725 participants. **IN PROGRESS**

a. Review interviews to determine eligibility for health screening
b. Schedule eligible participants for health screening

Task 7: Conduct health screening for 506 eligible participants. **IN PROGRESS**

a. Conduct 20-21 health screening sessions per week
b. Review test and interview results to determine eligibility for physical exam
c. Schedule eligible participants for physical examinations
d. Begin to track menstrual cycle of all eligible women

Task 8: Conduct physical exams of 186 eligible participants. **IN PROGRESS**

a. Conduct 8–9 physical examinations per week
b. Review results of exam to determine eligibility for medication-response testing
c. Schedule eligible participants for medication-response testing (scheduling women on Days 2 – 9 of their menstrual cycle)

Task 9: Conduct Medication Response (BAES screening) sessions for 186 eligible participants (82 men, 104 women). **IN PROGRESS**

a. Conduct medication-response session for 8-9 participants per week
b. Score BAES and identify participants eligible for ERP testing, using criteria specified in proposal
c. Schedule eligible participants for ERP testing sessions (scheduling women on Days 2–9 of their menstrual cycle)
d. Nurse practitioner continues to track menstrual cycle of all eligible women

Task 10: Test 96 eligible participants (48 men, 48 women) in two ERP sessions each **IN PROGRESS**

a. Conduct 7-8 ERP sessions per week
b. Ensure that a minimum of 48 h intervenes between the two ERP sessions for each participant
c. Nurse practitioner continues to track menstrual cycle of all eligible women until they complete two ERP sessions

Task 11: Process ERP data from first 192 ERP sessions (96 participants) **IN PROGRESS**

a. Back up data from each testing session, as described in the proposal
b. Execute blink correction algorithm, as described in proposal
c. Average ERP data for each participant within 24 h of testing session
d. Quantify ERP data for each participant within 72 h of testing session
e. Plot averaged ERP waveforms for each participant
f. Investigators review plots and quantified data for each participant

Problems. In the first year of the project, progress in obtaining HSRRB approval was slowed by the need to relocate our laboratory to space in a new building on the campus of the National Naval Medical Center. This relocation was required as a result of the Walter Reed Army Medical Center – National Naval Medical Center Base Realignment and Closure effort; and involved USU-sponsored renovations to accommodate electrophysiological recording and other aspects of this and our other research protocols. As noted in our first annual report, the laboratory is now completely re-established, and as we predicted, the new space accommodates this protocol more effectively than did the old space. Progress this year was facilitated by this renovation and no new problems have arisen in the conduct of the project.

Key Research Accomplishments

From the time the protocol was approved by the HSRRB (7/3/08) to the end of this reporting period (4/15/09), our focus has been on recruiting, screening, and testing participants, and on processing data obtained from these participants. Thus, the key research accomplishments are reflected in Table 1, which summarizes the number of participants who have completed each phase of the protocol. Data processing has largely kept pace with data collection.

The purpose of the web survey and the onsite health screening is to determine whether individuals meet the criteria for inclusion in the protocol. These criteria are designed to (1) minimize risk to participants and (2) maximize our ability to detect responder-group differences (i.e., to reduce heterogeneity). The purpose of the medication-response screening is to identify groups of individuals, using criteria developed in pilot studies in our laboratory, exhibiting a strong stimulant response to *d*-amphetamine and a group that does not exhibit this response (see Figure 1). We invite individuals falling into either of these two groups to participate in the ERP phase of the study.

Table 1. Participants Completing Each Phase of the Protocol

Phase of Study	Number of Participants
Respondents to recruitment notices	1,962
Eligible for web survey	832
Completed web survey	593
Eligible for health screening	455
Completed health screening	198
Eligible for medication-response testing	137
Completed medication-response testing	66
Completed first ERP session (only)	11
Completed both ERP sessions	22

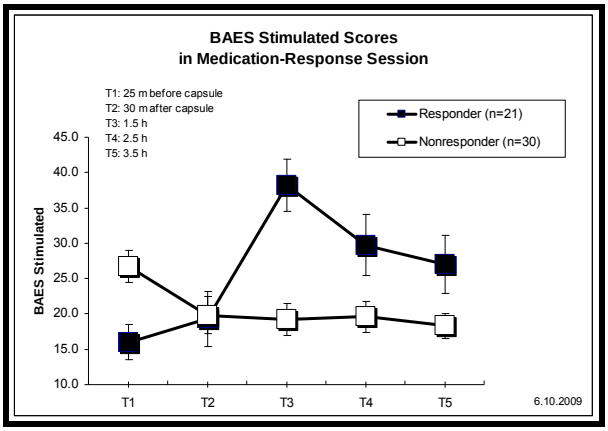

Figure 1. Mean scores on the Biphasic Alcohol Effects Scale for participants meeting criteria for inclusion in *Responder* and *Nonresponder* groups. The BAES is administered before and four times after administration of 10-mg *d*-amphetamine, to identify a group of individuals who report a strong stimulant response to that drug and a group of individuals who report no stimulant response. As is evident, we have successfully identified individuals meeting criteria for inclusion in these groups. We are in the process of testing individuals in these two groups in the ERP phase of the protocol (once following placebo and once following 10-mg *d*-amphetamine), while we also continue to identify individuals in these two groups.

Reportable Outcomes

We obtained HSRRB approval on 7/03/08. While we are now in the process of recruiting, screening, and testing participants, we have not yet collected sufficient data to analyze. We will present a summary of our progress on this project at the CDMRP-sponsored *Military Health Research Forum*, to be held in August in Kansas City, MO (see #1 below), by which time we anticipate having sufficient data to conduct preliminary data analyses. The other papers listed here (#2 and #3) do not report data collected under the auspices of this research grant. Rather, the papers are listed because they were completed during the project period and bear a conceptual relation to the current research, and because the work reported in the papers facilitated the development of the current protocol. The four applications for funding (#4 – #7) are listed because they benefited from the protocol development done for the current research; Items #6 and #7 were recently approved for funding.

1. Gabbay, F. H., Duncan, C. C., & Hall, E. C. Brain markers of risk for alcoholism. Accepted for presentation, *Military Health Research Forum*, Kansas City, MO, August, 2009.
2. McDonald, C. G., Gabbay, F. H., Rietschel, J. C., & Duncan, C. C. On processing novel stimuli: Does P3a stand alone? *Psychophysiology*, in press.
3. Gabbay, F. H., Duncan, C. C., & McDonald, C. G. Brain markers of amphetamine preference: Event-related brain potential indices of novelty processing distinguish amphetamine choosers and nonchoosers. In preparation.
4. *Negative Affect: A Shared Diathesis for Alcoholism, Drug Abuse, and PTSD*. (Under review, FY09 Peer-Reviewed Medical Research Program, Congressionally Directed Medical Research Program (CDMRP), Principal Investigator: Frances H. Gabbay, Ph.D.)
5. *Brain indices of novelty detection and reorienting: Articulating an endophenotype*. (Under review, National Institute on Drug Abuse, Principal Investigator: Frances H. Gabbay, Ph.D.)
6. *Brain Indices of Risk for PTSD after Mild TBI* (Funded, CDMRP, Principal Investigator: Connie C. Duncan, Ph.D.)
7. *Predicting Outcome after Mild TBI: Brain Indices of Structure and Function* (Funded, Department of Defense, Center for Neuroscience and Regenerative Medicine, Principal Investigator: Connie C. Duncan, Ph.D.)

Conclusion

We are continuing to recruit, screen, and test participants for the protocol. We have made important progress in data collection and processing, and are preparing to report preliminary analyses at the CDMRP-sponsored Military Health Research Forum in Kansas City (August 31 – September 3, 2009).